HEALTH ADVISORY

Missouri Department of Health and Senior Services

Paula F. Nickelson, Director **8 March 2024**

The Missouri Department of Health & Senior Services (DHSS) uses four types of documents to provide important information to medical and public health professionals, and to other interested persons:

Health Alerts convey information of the highest level of importance which warrants immediate action or attention from Missouri health providers, emergency responders, public health agencies, and/or the public.

Health Advisories provide important information for a specific incident or situation, including that impacting neighboring states; may not require immediate action.

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Phone: 800-392-0272
Fax: 573-751-6041
Web: health.mo.gov

Acinetobacter baumannii Bacteria with Combined NDM and OXA-23 Antibacterial Resistance Genes in Missouri

Summary

- In recent months, the Missouri Department of Health and Senior Services (MDHSS) has detected an increase in cases of Carbapenem resistant *Acinetobacter baumannii* (CRAB) with the combination of New Delhi metallo beta lactamase (NDM) and oxacillinase 23 genes (OXA-23) within health care facilities in Missouri. Acquisition of such genes by CRAB further increases antibacterial resistance of this bacteria and limits treatment options.
- This health alert provides background and epidemiological information on CRAB harboring NDM and OXA-23 genes and describes recommendations for facilities regarding infection prevention and control, transmission-based precautions, inter-facility communications, screening, laboratory testing, and reporting requirements in order to prevent spread of highly resistant organism among the state's health care facilities.

NDM and OXA-23 CRAB Background

Carbapenem Resistant *Acinetobacter baumannii* (CRAB) was classified as an urgent threat by the Centers for Disease Control and Prevention (CDC) due to enhanced transmissibility and limited treatment options (1). Patients with CRAB infection tend to have longer hospital stays and higher in-hospital mortality compared to those without CRAB infections. In the national retrospective cohort study of veterans with positive CRAB cultures, the 90-day mortality rate was as high as 30.3%. (2)
In another study, blood stream infections caused by multidrug resistant *Acinetobacter baumannii* were associated with high rates of septic shock and mortality among large tertiary-care hospital patients in Italy. (3)
The more common resistance genes in CRAB are OXA-23-like, OXA-24/40-like and OXA-58-like oxacillinases. A small proportion of CRAB possess mobile genes that encode different carbapenemases, such as KPC, IMP, NDM, VIM, and OXA-48-like. According to the CDC Antimicrobial Resistance and Patient Safety Portal, in 2022 there were only 125 detections of NDM gene in 6,131 (2.03%) isolates of *Acinetobacter baumannii* tested by the CDC Antimicrobial Resistance Laboratory Network (ARLN) across the United States (5).

CRAB with dual antibacterial resistance mechanism, where both OXA-23 and NDM genes are present, is very rare, and such combination further amplifies bacterial drug resistance.
Combined NDM and OXA-23 CRAB has previously been seen in the United States during an outbreak of NDM-CRAB in California between May 2020 and April 2021 with 79% of their isolates containing both NDM

and OXA-23 genes. (5) Overall, 85% of the tested isolates were pan-nonsusceptible to tested antimicrobials during that outbreak.

Risk Factors
CRAB mostly affects individuals with underlying conditions, those requiring prolonged or complex medical care, as well as those with indwelling devices and/or chronic wounds. Healthy people without these risk factors, including health care workers and family members, have a low risk for becoming infected with CRAB.

Transmission
CRAB can spread from one patient to another in hospitals, nursing homes, and other health care settings. People can be colonized with CRAB without displaying symptoms but still transmit the infection to other persons without proper infection control practices. It can spread through close contact with affected patients and contaminated surfaces or equipment. CRAB can live on surfaces for several weeks. Contact with these surfaces allows the organism to spread to other people. Once a patient has tested positive for CRAB infection or colonization, they are likely considered colonized for life and infection control measures should be utilized.

Infection and Colonization
CRAB can cause clinical infection in different parts of the body, such as in the bloodstream, open wounds, and urinary tract infections. The symptoms depend on the location and severity of CRAB infection. Symptoms are usually similar to bacterial infection presentation. There is not a common set of symptoms specific for CRAB infections. People can also get CRAB on their skin and other body sites without getting sick or having an active infection with symptoms. Health care providers may refer to this as 'colonization.' Some colonized persons may eventually develop clinical infection due to CRAB. Those who are colonized can still contaminate surfaces or objects they contact with CRAB, which can then spread it to other patients.

Diagnosis
Health care Providers can diagnose a patient as actively infected or colonized with CRAB in two ways:

- **Colonization screening–** a health care provider collects an axilla/groin swab and/or a rectal swab and sends the swab to a laboratory for testing.
- **Clinical specimen testing–** If a patient is showing symptoms of an infection of an unknown cause, a health care provider may collect a clinical sample, like, blood or urine, and the results may show that the patient has CRAB. Additional testing is done to determine if the carbapenemase genes are present.

Retesting patients infected or colonized with CRAB is not recommended and should not be used to change infection control measures. A negative test after a previous positive does not ensure that the patient no longer has CRAB on their skin or other body sites and will not spread it to others.

Treatment
Treatment is NOT recommended for persons colonized with CRAB, including NDM and OXA-23 positive CRAB. Those persons with clinical infection with CRAB susceptible to polymyxins should be managed in consultation with an infectious disease specialist. Patients with infection due to CRAB resistant to all antibiotics tested, including polymyxins, should be only managed with infectious disease expert consultation since no known effective therapy exists.

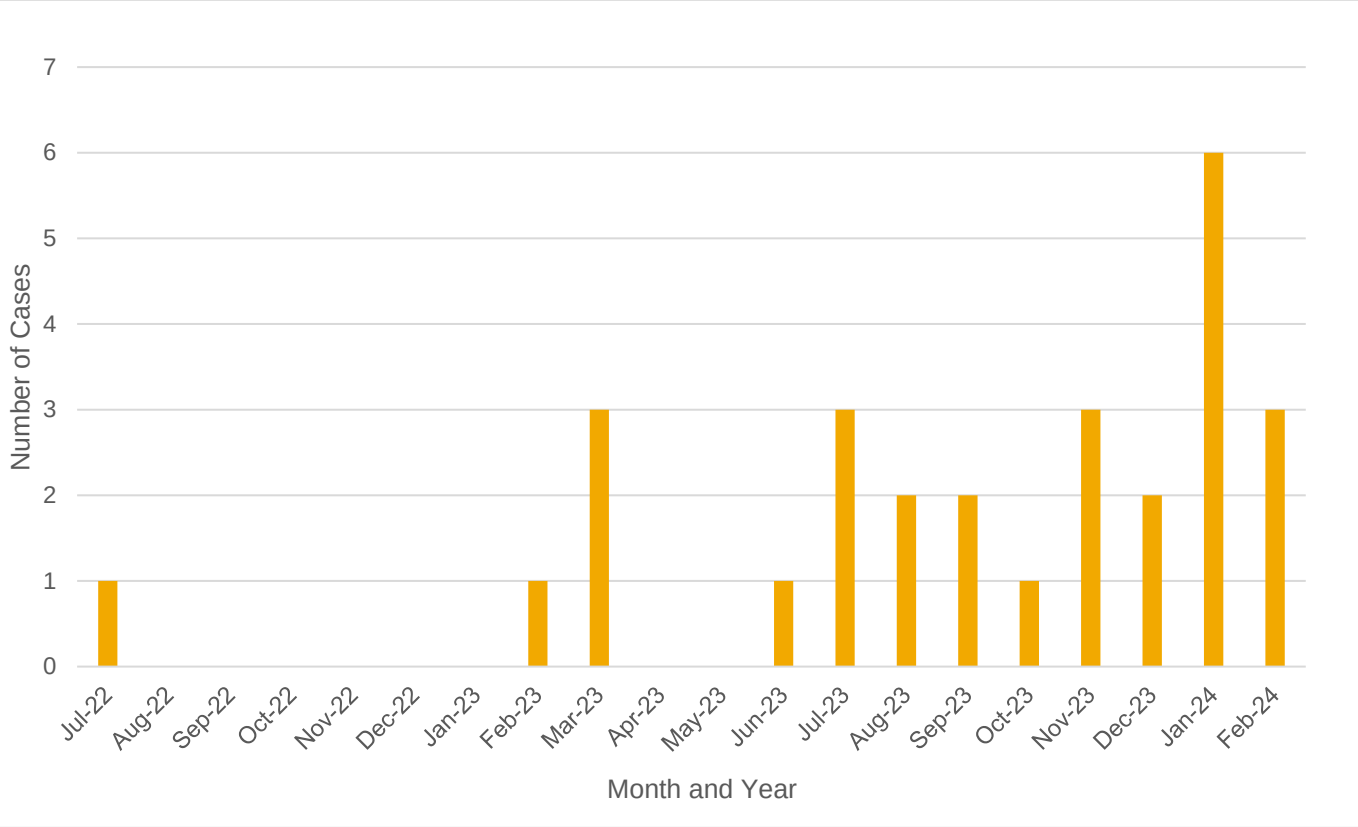
Epidemiology of NDM and OXA-23 CRAB in Missouri
NDM and OXA-23 gene containing CRAB was first seen in Missouri in July 2022. NDM and OXA-23 CRAB infection cases have been detected in a variety of health care facilities including Acute Care Hospitals and Skilled Nursing Facilities. Currently, cases have been identified in at least three regions in Missouri.

From the 28 cases reported in Missouri:

- Patient age ranges from 30 to 96 years old with a median age of 64.5 years.
- 74% of patients have been male.

- Clinical isolates were obtained from wounds, urine, sputum, blood, bone, bronchoalveaolar lavage/bronchial washing.
- All patients currently infected with NDM and OXA-23 CRAB resided in a skilled nursing facility or have had hospitalizations within the last 12 months.

Graph 1. Number of NDM and OXA-23 positive *Acinetobacter baumannii* cases by month, Missouri, 2022-2024*



*Feb-24 data is preliminary as of 03/8/2024

Missouri DHSS Recommendations

Infection Prevention and Control

The CDC and the MDHSS recommends health care facilities take the following actions to identify and control further spread:

- Immediately initiate and regularly reinforce appropriate use of transmission-based precautions based on the setting (described below).
- Inform and educate appropriate personnel about the presence of a patient with CRAB and the need for rigorous adherence to infection control practices.
- Ensure strict adherence to hand hygiene and appropriate personal protective equipment (PPE) use. Alcohol-based hand sanitizer is effective against CRAB and is the preferred method for cleaning hands when they are not visibly soiled. Wearing gloves is not a substitute for hand hygiene.
- Perform thorough cleaning and disinfection of the patient care environment and any shared equipment (daily and terminal cleaning) used by patients with CRAB. Use a disinfectant effective against

Acinetobacter baumannii. Some products may have a longer kill time for *Acinetobacter baumannii* please refer to product label or manufacturer.
- If possible, use dedicated medical equipment for patients with confirmed or suspected CRAB.
- Promote antimicrobial stewardship to limit the emergence of CRAB and other multi-drug resistant organisms (MDROs).

Transmission-Based Precautions

Health care facilities should not decline admission based on colonization or presence of MDRO infection including CRAB.
All patients with CRAB infection or colonization should be placed on the appropriate transmission-based precautions based on the setting:
- **Acute care hospitals, post-acute care facilities (including long-term acute care hospitals)** should place patients with CRAB on contact precautions.
- **Skilled Nursing Facilities** should place patients on Enhanced Barrier Precautions (when contact precautions do not otherwise apply). More information on enhanced barrier precautions can be found here: https://www.cdc.gov/hai/containment/PPE-Nursing-Homes.html
    - **Skilled nursing facilities with ventilator units,** should initially place patients on contact precautions. Patients may be able to be moved to Enhanced Barrier Precautions.
- **Dialysis clinics and providers** should care for patients with CRAB by having health care personnel wear disposable gowns and gloves during patient care or when touching items at the dialysis station. Gowns and gloves should be removed and disposed of carefully, and hand hygiene should be performed when leaving the patient's station. Minimize exposure to other patients by placing the patient away from others or seeing the patient at the end of day.
- **Outpatient Settings** should care for patients with CRAB by having health care personnel wear disposable gown and gloves if extensive patient contact is anticipated or contact with infected areas is planned (e.g., debridement or dressing of colonized or infected wound). Gowns and gloves should be removed and disposed of appropriately, and hand hygiene should be performed when leaving the patient's room.
- **Home Health care settings** should care for patients with CRAB by having health care personnel wear disposable gown and gloves when entering the area of the home where patient care is provided. Gowns and gloves should be removed and disposed of appropriately. Hand hygiene should be performed when leaving the patient care area. Minimize exposure to other patients by seeing the patient at the end of day.

Place all patients with confirmed or suspected CRAB infection or colonization in a private room. If a private room is not available:
- Patients infected or colonized with CRAB and/or other MDROs should be placed in rooms with patients colonized with the same organism(s). CDC does not recommend placing patients with CRAB in rooms with patients who have other types of MDROs.
- Avoid placing CRAB patients with patients who have indwelling devices (e.g., central venous catheter, tracheostomy tubes and mechanical ventilators), serious underlying medical conditions, or are otherwise immunocompromised.

MDHSS does not currently recommend the discontinuation of precautions for a patient or resident with a current, or history of, CRAB colonization or infection.

Interfacility Communication
Robust communication at the time of transfer ensures the continuation of infection prevention and control measures during transitions of care. This can be accomplished via verbal report at the time of transfer, in the discharge summary, or with an interfacility transfer tool.
- Upon admission, ask about a patient's CRAB and other MDRO status, if not included in the accompanying medical records.

- Upon admission, assess CRAB and other MDRO status for all patients by reviewing medical records and utilizing EHR or HL7, especially for patients being admitted from long term acute care hospitals or from ventilator units.
- Upon discharge, communicate a patient's CRAB and other MDRO status, including for any patients screened for an MDRO, but for whom laboratory results are not available at the time of transfer, to any receiving health care facility prior to transfer.
    - This should be done by including a written notification of the infection or colonization to the receiving facility in transfer documents. The referring facility should ensure that the documentation is readily accessible to all parties involved in patient transfer (for example, referring facility, medical transport, emergency department, receiving facility). CDC has a sample Interfacility Transfer Form that facilities can use.

Containment Response
A single case of CRAB (active infection or colonization) requires a robust containment response. Be aware that as part of the current investigation the MDHSS Healthcare Associated Infections/Antimicrobial Resistance (HAI/AR) Program may be conducting outreach to health care facilities and clinical laboratories with epidemiologic links to case patients or health care facilities with cases of CRAB infection.

Colonization Screening[1]
MDHSS recommends screening patients for carbapenemase producing CRAB who meet any of the following criteria:

- Patients presenting from long-term acute care facilities, skilled nursing facilities, or rehabilitation facilities, within the past 12 months, and have history of:
    - Multi-drug resistant organisms (MDROs)
    - Mechanical ventilation or tracheostomy
    - Chronic or unhealing wounds
- Patients hospitalized outside of the United States within the preceding 12 months

Testing of the environment or equipment for *Acinetobacter baumannii* is not routinely recommended. Likewise, testing of health care workers or family members who care for patients with CRAB (or an exposure to CRAB) is not routinely recommended.

Clinical Laboratories
The Missouri State Public Health Laboratory (MSPHL) continues to request clinical laboratories submit CRAB isolates from residents receiving health care in Missouri as outlined below:

- Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) that are resistant to imipenem, meropenem, or doripenem using current CLSI breakpoints (i.e., minimum inhibitory concentrations of >8 mcg/ml)
    - Please send pure isolates only AND a copy of your clinical laboratories AST results so that we may ensure suitable criteria.

MSPHL, as part of a national surveillance program, can provide testing for carbapenemase genes. MSPHL methods for testing include: mCIM, and PCR markers (KPC, NDM, VIM, OXA-48-like, IMP, OXA-23-like, OXA-24-like, and OXA-58-like genes).

Reporting
Health care facilities, providers, and laboratories with suspected or confirmed cases of CRAB (active infection or colonization), should report them to the MDHSS HAI/AR Program at 573-751-6113 or the MDHSS Emergency Response Center (ERC) at 800-392-0272. Carbapenemase producing organisms including *Acinetobacter*

[1] Colonization testing (screening) for *C. auris* and carbapenem-resistant bacteria, including *Acinetobacter baumannii* is available at no cost through the CDC Antimicrobial Resistance Laboratory Network. These services can be accessed in consultation with the MO DHSS by contacting the Healthcare Associated Infections/Antimicrobial Resistance (HAI/AR) Program.

baumannii is implicitly reportable in Missouri as an emerging or unusual disease per State of Missouri regulations, 19 CSR 20-20.020, *Reporting Infectious, Contagious, Communicable, or Dangerous Diseases*). Carpabenemase producing organisms are nationally notifiable as of 2023.

Please contact the MDHSS HAI/AR Program for:

- Patients newly colonized or infected with CRAB (immediately notifiable)
- Guidance on CRAB screening of roommates or other close contacts
- Guidance on patient cohorting (i.e., grouping patients infected with the same infectious agents together to confine their care to one area and prevent contact with susceptible patients)
- Guidance on infection control interventions
- HAI Surveillance including reporting, specimen collection, and specimen submission to the MSPHL.

The MDHSS HAI/AR Program can be contacted at the following 573-751-6113 or the MDHSS Emergency Response Center (ERC) at 800-392-0272. Email address: info@health.mo.gov

References

1. CDC. (2019). Carbapenem Resistant Acinetobacter https://www.cdc.gov/drugresistance/pdf/threats-report/acinetobacter-508.pdf
2. Vivo et al. BMC Infectious Diseases (2022) 22:491 https://doi.org/10.1186/s12879-022-07436-w)
3. Russo A, et al. Bloodstream infections caused by carbapenem-resistant Acinetobacter baumannii: Clinical features, therapy and outcome from a multicenter study. J Infect. 2019 Aug;79(2):130-138. doi: 10.1016/j.jinf.2019.05.017.)
4. CDC. (2023, June) Carbapenem-Resistant Acinetobacter baumannii, Antimicrobial Resistance & Patient Safety Portal
5. California Department of Health.(2021, February) Regional Outbreak of Highly Drug-resistant Carbapenemase-producing Acinetobacter baumannii https://www.cdph.ca.gov/Programs/CHCQ/HAI/CDPH%20Document%20Library/CAHAN_NDM_OXA23_CRAB_May2021.pdf

Target Audience

Local Health Departments, Infectious Disease Physicians, Hospital Emergency Departments, Infection Control Preventionists, Health Care Providers, Long Term Care Facilities, Dialysis Clinics, and Laboratories

Author

MDHSS Healthcare Associated Infections/Antimicrobial Resistance Program, the State Epidemiologist, and Division of Community and Public Health.

This information is current as of March 5, 2024 but may be modified in the future. We may continue to post updated information regarding the most common questions about this subject.

HEALTH ADVISORY

Missouri Department of Health and Senior Services

Paula F. Nickelson, Director

18 April 2024

Health Risks Associated with *Hemp-Derived Intoxicating Cannabinoids*

The Missouri Department of Health & Senior Services (DHSS) uses four types of documents to provide important information to medical and public health professionals, and to other interested persons:

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Summary

- The recent amplified availability and use of Hemp-Derived Intoxicating Cannabinoids (e.g., delta-8 tetrahydrocannabinol (THC) and over a dozen others) pose significant health risks, particularly to youth.
- Reporting of adverse reactions to consumption of products containing Hemp-Derived Intoxicating Cannabinoids has increased.
- These intoxicating compounds are currently untested in humans, unregulated, and sold to the public without restriction.
- Until safety data is available for human consumption, Missourians are advised to avoid these products.

Background

Hemp-Derived Intoxicating Cannabinoids are not currently subject to federal regulation.

- The 2018 Farm Bill legalized hemp but included “derivatives” and “isomers” of the plant in the definition of hemp, as long as content of delta-9 THC by weight is less than 0.3%.
- Since 2018, processes have been developed to chemically derive over a dozen different intoxicating cannabinoids from hemp at varying potency levels.
- Hemp is indeed regulated by the U.S. Dept of Agriculture, but that regulatory authority ends after harvest. There is no safety/quality/concentration regulation pertaining to hemp subject to post-harvest chemical conversions.
- The FDA views hemp-derived cannabinoids as unapproved food additives, unapproved new drugs, misbranded drugs, adulterants when in food, and excluded from the definition of dietary supplements. The FDA has issued numerous warning letters to food facilities documenting violations of these regulations after the 2018 Farm Bill, including letters sent as recently as November 2023.

Hemp-Derived Intoxicating Cannabinoids are also not currently subject to state regulation in Missouri.

Currently, a wide variety of foods, beverages, purported dietary supplements, and other commodities containing hemp-derived compounds, both intoxicating and non-intoxicating, are available online and in traditional brick-and-mortar establishments in Missouri.

These products are marketed progressively and assertively in eye-catching ways to attract public consumption, particularly that of young consumers.

11.4% of 2,186 US 12-grade students self-reported Delta-8-THC use in 2023, and this prevalence was noted to be higher in the Midwest, according to a recent March 12, 2024, publication in the Journal of the American Medical Association (Harlow, et al.).

Risk Factors

Consuming Hemp-Derived Intoxicating Cannabinoids is associated with the following risks:

Risk for Poisoning

- There are no studies on human health effects and safety of these compounds.
- Both short-term and long-term effects of these compounds are unknown.
- Many products include a combination of these new intoxicating cannabinoids.
- Many products are mislabeled, alleging inaccurate potency, and not disclosing presence of combinations of intoxicating cannabinoids or other toxic byproducts or contaminants.
- There are no regulated potency limits, despite risk of higher potency leading to greater harm.
- Accidental poisoning to children is due to attractive packaging and lack of childproofing.
- U.S. Poison Centers reported 82% more delta-8-THC cases in 2022 compared to 2021.

Potential for Unexpected Intoxication

- There are no standards requiring products containing hemp-derived compounds to disclose the amounts of intoxicating cannabinoids in the product. One recent study found at least twenty-six different intoxicating compounds in hemp-derived cannabis products readily available on the market, the most common being Delta-8 tetrahydrocannabinol (THC), THC-P, Delta-9 THC, HHC, THC-A, Delta-10 THC, THC-H, THC-B, THC- JD, THC-X, HHC-P, and Delta-11 THC.
- Because there are large variations in product formulation and widespread inaccuracies in labelling of active ingredient content, percentage, and/or quality, the consumer cannot have confidence in the dosage of hemp-derived compounds being ingested, even when attempting to make an informed decision based on the label.

Appeal to Children and Mimicking of Commercial Food Products

- There are no regulations imposing age restrictions on intoxicating hemp-derived products, which are widely available online and in brick-and-mortar establishments like gas stations, grocery stores, and convenience stores. Some of these intoxicating hemp-derived products intentionally mimic commercial food products that appeal to children.

Direct effects of these particular cannabinoids on the body include but are not limited to the following:

- Impairment of cognitive function, memory, and judgment. Hallucinations. Anxiety.
- Nausea, vomiting.
- Dizziness, tremor.
- Loss of consciousness, death.
- Dependency: Prolonged use may result in dependency, leading to addiction and withdrawal symptoms.

Impaired driving and operation of machinery, increasing risk for lethal accidents.
Contaminants and byproduct effects on the body

- Chemically processing hemp into intoxicating cannabinoids can involve the use of toxic solvents and acids, which can remain in the final product.

Processing hemp into intoxicating cannabinoids without testing may result in products with high concentrations of heavy metals, infectious contaminants, and other contaminants, such as mold and pesticides.

Context
Intoxicating cannabis-related compounds can be divided into at least 4 categories:

	Category	Availability
1	**Marijuana/Cannabis** Naturally occurring intoxicating compounds contained within Cannabis indica, Cannabis sativa, and Cannabis ruderalis. Although these plants contain over 480 constituents, delta-9-THC is assumed to be the main ingredient that generates the intoxicating effect.	Adult recreational cannabis is legal in Missouri for ages 21 and up, only at cannabis dispensaries, regulated by the MO Department of Health and Senior Services – Division of Cannabis Regulation. Medical cannabis is regulated separately for eligible individuals by the same agency.
2	**Hemp-Derived Intoxicating Cannabinoids** *Chemically derived* psychoactive compounds processed from hemp, including but not limited to **Delta-8 THC**, Delta-6 THC, Delta-10 THC, Delta-11 THC, THC-A, THC-O, THC-P, THC-V, THC-JD, PHC, HHC, HHC-P and HXC. These compounds are also referred to as "Derived Psychoactive Cannabis Products" (DPCPs).	These products are progressively available to the public at commercial venues without age restrictions or any other health and safety regulations.
3	**Synthetic Cannabinoids** Chemically engineered molecules that do not necessarily resemble the cannabinoid molecular structure but that nevertheless trigger the cannabinoid receptors. Also referred to as "Designer Synthetic Drugs." Ex: K2 or Spice.	These are illegal drugs sold on the black market.
4	**Pharmaceutical Cannabinoids** FDA-approved pharmaceutical cannabinoids for targeted health conditions. Ex: dronabinol (brand name Marinol)	Available by prescription only. Classified as Schedule III drugs under the Controlled Substances Act.

Missouri DHSS Recommendations

In 2021, DHSS joined CDC in issuing a Health Advisory that warned the public to be aware of concerns with Hemp-Derived Intoxicating Cannabinoids. Since then, Missouri has experienced an increase in cannabis consumption poisonings and has identified reliable evidence of unique health and safety risks associated with these products. At this time, the public should avoid products that contain Hemp-Derived Intoxicating Cannabinoids until further notice. Without additional research regarding safety in humans, these compounds are considered unsafe.

Youth are particularly susceptible to these readily available products. These products should vigilantly be kept out of reach of children and pets.

Sale of these products in Missouri is discouraged until safety data is available in order to protect the public health of Missourians. If direct-to-consumer availability persists, retailers are strongly encouraged to ensure the products they sell have been tested for contaminants, to only sell products that accurately disclose potency

information, to clearly label products with a warning that the product has not been determined to be safe or effective, to avoid making any medical claims about the product's use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and to prohibit sales to youth under 21 years of age.

Product labels should be checked when possible to identify and avoid the following product ingredients, which are Hemp-Derived Intoxicating Cannabinoids if sold outside of a Missouri-regulated cannabis dispensary: Delta-8 THC, Delta-6 THC, Delta-10 THC, Delta-11 THC, THC-A, THC-O, THC-P, THC-V, THC-JD, PHC, HHC, HHC-P and HXC. However, it is important to note there is no regulatory authority verifying these product labels are accurate.

Further awareness-raising and education is warranted to inform the public in Missouri.

Healthcare providers should screen patients for all types of cannabinoid use and provide appropriate interventions for those at risk. Patients presenting with cannabis intoxication symptoms who do not report cannabis use should be queried about their exposure to Hemp-Derived Intoxicating Cannabinoids and managed accordingly.

For additional information on Hemp-Derived Intoxicating Cannabinoids: Refer to the References listed below.

References

- MO DHSS: https://health.mo.gov/safety/cannabis/pdf/hemp-derived-cannabinoids.pdf
- CDC: Increases in Availability of Cannabis Products Containing Delta-8 THC and Reported Cases of Adverse Events https://emergency.cdc.gov/han/2021/pdf/CDC_HAN__451.pdf
- DEA: https://www.dea.gov/sites/default/files/2020-06/Marijuana-Cannabis-2020_0.pdf
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- University of North Texas Health Science Center at Fort Worth School of Public Health – Dr. Matthew Rossheim https://www.unthsc.edu/school-of-public-health/derived-psychoactive-cannabis-products-dpcps/

Target Audience
Local Health Departments, Hospital Emergency Departments, Health Care Providers, First Responders, Poison Control Centers, Laboratories and the Public.

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HEALTH ADVISORY

Missouri Department of Health and Senior Services

Paula F. Nickelson, Director **14 May 2024**

Alpha-gal Syndrome: Important Information for Missouri Healthcare and Public Health Professionals

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Summary

Alpha-gal Syndrome (AGS) is an emerging, tick bite-associated allergic condition characterized by an immunoglobulin E (IgE)-mediated hypersensitivity to galactose-alpha-1,3-galactose (alpha-gal), a sugar molecule found in most non-primate mammalian meat and products derived from these mammals. It is also known as mammalian meat allergy, alpha-gal allergy, red meat allergy, and tick bite meat allergy. AGS is a serious and potentially life-threatening allergic condition, with symptoms and severity varying among persons. Symptoms generally appear 2-6 hours after eating foods or exposures to other products containing alpha-gal. Persons with AGS may have reactions that range from mild hives to severe and life-threatening anaphylaxis. Evidence suggests that AGS is primarily associated with the bite of the lone star tick, *Amblyomma americanum* in the United States. No cure is currently available; therefore, early identification and preventive efforts are the mainstay of addressing AGS.

A recent national survey of mostly primary care physicians in the U.S. found 78% of providers have little to no knowledge of AGS, and only 5% felt “very confident” in their ability to diagnose or manage patients with AGS.[1] The survey findings raised concerns for a delayed or missed diagnosis and incorrect patient management. Nearly 10% of patients diagnosed with idiopathic anaphylaxis were later found to have AGS.[2] Alpha-gal-specific IgE (sIgE) antibody testing results processed by the commercial laboratory responsible for nearly all testing in the United States before 2022 suggested that suspect cases predominantly occurred in counties in states located within the southern, midwestern, and mid-Atlantic U.S. regions, including Missouri.[3] Therefore, the Missouri Department of Health and Senior Services (DHSS) is issuing this Health Advisory to raise awareness of AGS and provide up to date information and resources to Missouri’s healthcare providers.

Background

AGS is not caused by an infection, but rather an (IgE)-mediated allergic condition which has been reported worldwide since 2007. People can get AGS after being bitten by a tick. The lone star tick (Fig 1.) can transmit alpha-gal to people through its saliva, which can trigger the immune system to produce IgE antibodies against alpha-gal causing AGS.[4, 5]

As a result, affected persons become very sensitive to an alpha-gal sugar molecule found in red meat and dairy products. A recent study found substantial epidemiologic evidence implicating a tick bite as a risk factor for AGS.[5] Patients with AGS were more likely than controls to report a tick bite, to have more ticks found on their bodies, and to have found more embedded ticks on their bodies before developing AGS.[5]

The exact mechanism, causal relationship, and risk factors associated with the development of AGS are currently unknown. The induction of alpha-gal sIgE by a tick bite is thought to be a key event in the development of AGS. In some persons, tick bites result in the development of sIgE antibodies in the absence of clinically apparent AGS resulting in a state referred to as **sensitization**. It is not known why some people develop alpha-gal sIgE but do not present with AGS, so other intrinsic factors may also play a role. It is also possible a single tick bite may result in sensitization, but that repeated tick bites could be required for some persons to develop AGS.[5]

Figure 1. Lone star Tick.[4]

The lone star tick is thought to be the most likely culprit related to AGS in the U.S., but a link to other kinds of ticks has not been ruled out. A temporal and geographic alignment of the onset of AGS and state of residence with the seasonal timing of the lone star tick activity and the known geographic distribution of the lone start tick respectively has also been reported.[3,5] The lone star tick is a well-known vector for tickborne illnesses in the U.S. including ehrlichiosis and tularemia. Missouri is among the states with the highest rates of ehrlichiosis and tularemia cases. Consequently, it is not unexpected that Missouri is among the states with the highest prevalence of sIgE-positive persons and AGS (Fig 2).[3]

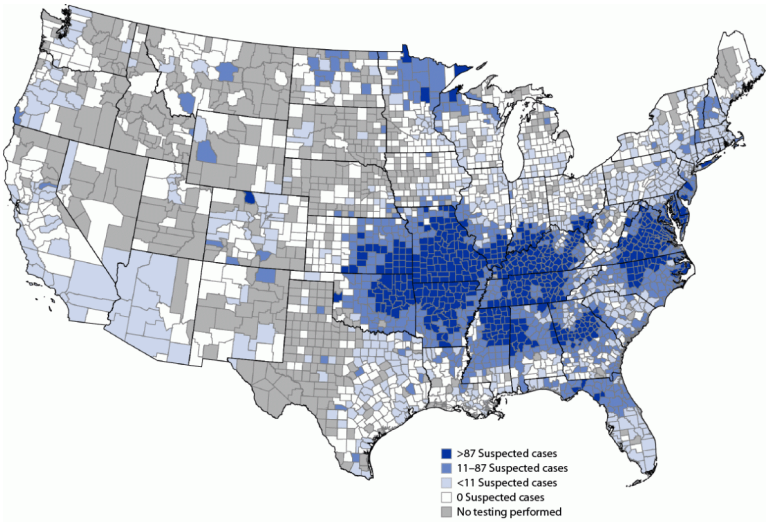

Figure 2. Geographic distribution of suspected alpha-gal syndrome cases per 1 million population per year — United States, 2017–2022.[3]

Clinical Presentation

AGS is characterized by a delayed onset allergic reaction following ingestion of mammalian meat or its derivatives. Unlike other food allergies, the symptoms often appear delayed for 2-6 hours after eating or other exposures to products containing alpha-gal.[6] Exposures to alpha-gal commonly include beef, pork, lamb, or meat from other mammals, as well as many other foods, including dairy products, medications, and medical products made using materials from mammals. Some foods and medications contain gelatin, which is often made from mammal-derived collagen or other materials from animals. Symptom onset is more rapid with intramuscular or intravenous exposures, such as from some medical products (e.g., certain monoclonal antibodies, heparin, antivenom).[6]

The clinical spectrum of AGS is broad with symptoms ranging from urticaria and gastrointestinal distress to angioedema and life-threatening anaphylaxis. The mucocutaneous signs and symptoms were found to be the most common, with hives/urticaria being most frequently reported followed by gastrointestinal symptoms.[6] Respiratory or cardiovascular symptoms were less frequently reported. AGS reactions can vary from person to

person and in some persons may not occur after every alpha-gal exposure. Approximately 75% of patients identified as having AGS met the criteria for anaphylaxis with a symptom profile that was distinct from other food allergies.[6]

The symptoms of AGS reaction can include[4]:

- Hives or itchy rash
- Nausea or vomiting
- Heartburn or indigestion
- Diarrhea
- Cough, shortness of breath, or difficulty breathing
- Drop in blood pressure
- Swelling of the lips, throat, tongue, or eye lids
- Dizziness or faintness
- Severe stomach pain

Diagnosis

AGS is diagnosed by an allergy specialist or other healthcare provider through a detailed patient history, physical examination, a blood test that looks for specific antibodies, and follow-up evaluation after the AGS exposure has been removed. There is no definitive sIgE level that confirms AGS diagnosis. Tested persons can have sensitization to alpha-gal without clinical reactivity, and only a fraction of patients with alpha-gal sIgE experience symptoms with meat ingestion.[8] Currently, blood test levels of alpha-gal sIgE of ≥ 0.1 kU/L are considered positive.[3,5,6] The clinical relevance of the higher proposed cut-off value of 0.35 kU/L remains unclear.[8] Tests for alpha-gal sIgE are available at several large commercial laboratories and may be available at certain academic institutions. Even though the presence of alpha-gal sIgE is an established diagnostic criterion, levels do not correlate directly with symptoms or disease severity.[6,7,9] Even more challenging is that **asymptomatic alpha-gal sensitization is known to occur, so not all patients who test positive for alpha-gal sIgE will have AGS**. For example, the sensitization rate was found to be 22% among a cohort of patients undergoing endoscopy without a history of AGS in North Carolina,[10] while an asymptomatic cohort in Tennessee showed a sensitization rate of 20.8%.[11] Additionally, a study conducted in Germany to characterize the prevalence of alpha-gal sIgE positivity among forest service employees and hunters found that 35% were sensitized to alpha-gal, but only 8.6% reported clinical symptoms of AGS.[12] Published data also demonstrated that among random cohorts of subjects in TN, VA, and NC 15% or more of the population have IgE to alpha-gal.[13] In such populations with high alpha-gal sensitization rates, the alpha-gal sIgE ≥2 IU/ml or >2% of the total IgE makes the AGS diagnosis more likely.[13] Measuring total IgE is helpful because some cases are non-atopic and have low total IgE.

The anti-alpha-gal IgE diagnostic assay can lead to false-positive results in those individuals where alpha-gal IgE sensitization may be related to bee and wasp stings, parasitism, atopy, or cat ownership, creating cases where these antibodies do not match the clinically pathognomonic history of AGS.[8] Thus, the alpha-gal sIgE testing is a helpful diagnostic tool but cannot be relied on solely for a diagnosis. Skin tests documenting a reaction to certain allergens (such as pork or beef) may also be used to diagnose AGS.[4,7]

Management

The management of patients with AGS generally requires a multi-faceted, patient-centered approach, including prevention of additional tick bites, antihistamine use, a diet void of mammalian meat and products derived from mammals to avoid allergic reactions, and follow-up visits with a healthcare provider. Patients experiencing an anaphylactic reaction require emergent medical care.

Not all patients with AGS have reactions to every ingredient containing alpha-gal. Mammalian meat (such as beef, pork, lamb, venison, rabbit, etc.) can contain high amounts of alpha-gal. Certain cuts of meat may contain more

than others. Because around 5% to 29% of people with AGS may have allergic reactions to dairy products (which contain alpha-gal, though at lower levels than meat), food products that contain milk and milk products may need to be avoided.[6] Some patients with AGS may be able tolerate milk products. Although very rare, some people with severe AGS may react to ingredients in certain vaccine types/brands (lists of additives to specific vaccines, called vaccine excipients, are available through CDC's Pink Book[14]) and medications/products that contain gelatin, glycerin, magnesium stearate, and bovine extract. Other medical products such as heart valves from pigs or cows, monoclonal antibodies, heparin, and certain antivenoms are animal-derived and may also contain alpha-gal. Persons suspected for AGS should read food and medicine product labels carefully.[15]

People with AGS who need to avoid eating meat from mammals can continue to eat chicken, turkey, fish, and other non-mammalian meats because those meats do not contain alpha-gal. It is important to consider that many varieties of sausages use casings derived from pork gut, such as chicken and turkey sausages, and consumption may induce anaphylactic or other reactions.[13] As with any severe allergy, patients with AGS should work with their healthcare providers to make decisions about individual risks and benefits from specific medications/vaccines. There is no clear evidence to indicate how long patients must maintain avoidance before adding back alpha-gal-containing products, but many report having to avoid alpha-gal for years. Over time, in the absence of repeated tick-bite exposures, the level of IgE antibodies against alpha-gal may decrease, and, as a result, some people with AGS may again be able to consume beef, pork, and other mammalian meats and other products that contain alpha-gal without having an allergic reaction. Spontaneous resolution of AGS is more likely in those who avoid additional tick bites and experience a decline in alpha-gal sIgE levels over time. All patients should receive personalized guidance on management of their AGS under the direct supervision of their qualified healthcare provider.

Prevention

Taking steps to prevent tick bites is crucial to reduce the risk of the development and persistence of AGS. For patients with a history of AGS, additional tick bites may heighten or reactivate allergic reactions to alpha-gal. Repeated lone star tick bites (or bites from other species of ticks associated with AGS in other parts of the world) can cause IgE antibody levels to rise or prevent them from decreasing. **Preventing tick bites is also an important measure to reduce the risk of other tickborne illnesses diagnosed in Missouri including ehrlichiosis, Rocky Mountain spotted fever, tularemia, Heartland virus, Bourbon virus, and Lyme disease.** Additional information regarding tickborne illnesses in Missouri is available on Missouri's Tickborne Disease Story Map.[16]

It is important to consider the following information and guidance for the prevention of tick bites.

- Whenever possible, avoid grassy, brushy, and wooded areas, where ticks may be found.
- When hiking, walk in the center of trails.
- Use Environmental Protection Agency (EPA)-registered insect repellents[17] on any exposed skin. EPA-registered active ingredients such as DEET and picaridin are widely available.
- Treat clothing and gear with products containing 0.5% permethrin. Treated items will remain protective through several washings. Alternatively, you can buy pre-treated clothing and gear.
- After being outdoors, carefully check your clothing, gear, and pets for ticks.
- Whenever possible, shower and change clothes soon after spending time outdoors.
- If you see an attached tick, remove it immediately.

Surveillance and Reporting

In 2022, a national surveillance case definition was developed for AGS to provide a set of uniform criteria for public health surveillance.[18] Surveillance case definitions enable public health officials to classify and count cases consistently across reporting jurisdictions. Surveillance case definitions are not intended to be used for the purposes of making a diagnosis or for decisions regarding treatment. AGS is not included on the Nationally

Notifiable Condition List and is not a reportable disease/condition in Missouri. AGS is however, an important public health concern that is impacting Missourians. In addition to increasing awareness and information regarding AGS to medical providers, DHSS continues to be active participants in the national discussion regarding AGS. Missouri DHSS is also monitoring developments in AGS research and continues to evaluate the feasibility of heightening surveillance efforts for AGS in Missouri.

Additional Information

For additional information on AGS, visit CDC's AGS website[4], the references provided, and/or seek consultation with a healthcare provider specializing in Allergy and Immunology. Missouri healthcare providers can contact their local public health agency or the DHSS's Bureau of Communicable Disease Control and Prevention at 573-751-6113 with questions regarding this Health Advisory.

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